PB82-241795

Sensitivity Analysis on Coburn Model Predictions of COHB Levels Associated with Alternative CO Standards (EPA Staff Paper)

(U.S.) Environmental Protection Agency
Research Triangle Park, NC

Jul 80

U.S. Department of Commerce
National Technical Information Service
NTIS

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO.
		PB82 241795

4. TITLE AND SUBTITLE
Sensitivity analysis on Coburn Model predicitons of COHb levels associated with alternatice CO standards

5. REPORT DATE
July, 1980

6. PERFORMING ORGANIZATION CODE

7. AUTHOR(S)

8. PERFORMING ORGANIZATION REPORT NO.

9. PERFORMING ORGANIZATION NAME AND ADDRESS
Strategies and Air Standards Division
Office of Air Quality Planning and Standards

10. PROGRAM ELEMENT NO.

11. CONTRACT/GRANT NO.

12. SPONSORING AGENCY NAME AND ADDRESS
US EPA
Research Traingle Park, NC 27711

13. TYPE OF REPORT AND PERIOD COVERED

14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES

16. ABSTRACT

In the June 1, 1979 draft staff paper presented to the Clean Air Scientific Advisory Committee, EPA included a table depicitng carboxyhemoglobin (COHb) responses to CO exposures as predicted by the Coburn Model. This table presents baseline or nominal estimates of the COHb levels expected to be achieved by non-smokers to constant CO concentrations for 1 to 8 hours.

Uncertainties exist, however, in using these estimates to decide which standards provide an adequate margin of saftey. First, even among normal person variations exist in the physiological parameters used in the Coburn model. These variations are sufficient to provide noticalbe deviations from the COHb levels that were predicted using normal parameters. EXen more substantial variations in these parameters are observed in population groups such as anemics that may be more sensitive to CO exposure. Second, predicitons based on exposure to constant CO concentrations inadequately represent the response of individual exposed to widely fluctuating concentrations that typically occur in ambient exposure situations.

An attempt was made to represent these uncertainties by performing a sensitivity analysis unsing the Coburn model in a dynamic mode to predict the COHb responses to specific patterns of fluctuating ambient concentrations of CO for individuals with physiological parameters different from the baseline values. The results of this analysis are given.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Carboxyhemoglobin (COHb) CO exposure Coburn model		EPA 68A

'BUTION STATEMENT	19. SECURITY CLASS *(This Report)*	21. NO. OF PAGES
	20. SECURITY CLASS *(This page)*	22. PRICE

0-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

PB82-241795

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA 22161

SENSITIVITY ANALYSIS ON COBURN MODEL PREDICTIONS OF COHB LEVELS ASSOCIATED WITH ALTERNATIVE CO STANDARDS

EPA STAFF PAPER

In the June 1, 1979 draft staff paper (1) presented to the Clean Air Scientific Advisory Committee (CASAC), EPA included a table depicting carboxyhemoglobin (COHb) responses to CO exposures as predicted by the Coburn model (2). An abbreviated version of that table is included in this paper (Table 1).

This table presents baseline (average) or nominal estimates of the COHb levels expected to be achieved by non-smokers to constant CO concentrations for 1 to 8 hours.

Uncertainties exist, however, in using these estimates to decide which standard provides an adequate margin of safety. First, even among normal persons variations exist in the physiological parameters used in the Coburn model. These variations are sufficient to provide noticeable deviations from the COHb levels in Table 1 that were predicted using baseline or nominal parameters. Even more substantial variations in these parameters are observed in population groups such as anemics that may be more sensitive to CO exposure. Second, predictions based on exposure to constant CO concentrations inadequately represent the response of individuals exposed to widely fluctuating concentrations that typically occur in ambient exposure situations.

Ott and Mage (3) investigated this point using an empirically derived CO uptake model to estimate COHb responses as a function of time for actual 1-hour average CO air quality data measured over a 12-month period in San Jose, California. Their calculations indicated that the assumption of a constant CO concentration for an 8-hour averaging time tends to underestimate the COHb response to CO concentrations that are actually fluctuating on a much shorter time scale.

Table 1

COHb Response to Constant CO Exposures

% COHb Based on Coburn Equation[a]

CO (ppm)	Exposure Time (Hours)			
	1		8	
	Intermittent Rest/Light Activity	Moderate Exercise	Intermittent Rest/Light Activity	Moderate Exercise
7.0	0.7	0.7	1.2	1.2
9.0	0.7	0.8	1.4	1.5
12.0	0.8	1.0	1.8	1.9
15.0	1.0	1.1	2.2	2.4
20.0	1.1	1.4	2.9	3.1
25.0	1.3	1.6	3.6	3.8
35.0	1.6	2.1	4.9	5.2
50.0	2.2	2.9	7.0	7.6

[a]Assumed parameters: V_A (Alveolar ventilation rates): intermittent rest/light activity = 10 L/min, moderate activity = 20 L/min (equivalent to 3 mph walk on level ground or light industry or housework); Hb (hemoglobin) = 15 g/dL (normal male); altitude = sea level; initial COHb level = 0.5 percent (normal level due to endogenous CO production); V_{CO} (endogenous CO production rate) = 0.007 mL/min (normal); V_b (blood volume) = 5500 mL (normal male); M (relative affinity constant of hemoglobin for CO and O_2) = 218; $D_{L_{CO}}$ (lung diffusivity for CO) = 30 mL/(min-mm Hg) (nominal)

The likely reason for this underestimation is that a peak in a series of overlapping 8-hour average CO concentrations tends to occur just after a period of rising 1-hour concentrations. As a result, the most recent CO levels at the time the 8-hour peak is reached are higher than the peak 8-hour average concentration. The high 1-hour CO levels result in higher COHb levels than would be predicted from an assumption of a lower 8-hour constant CO level corresponding to the peak 8-hour average concentration. This situation is illustrated in Figure 1 which shows two typical cases in which peak 8-hour average CO concentrations are preceded by higher 1-hour averages. It is noted that the estimated peak COHb level in persons exposed to these CO levels occurs between the peak 1-hour and 8-hour concentrations, demonstrating the strong influence of the 1-hour peak values.

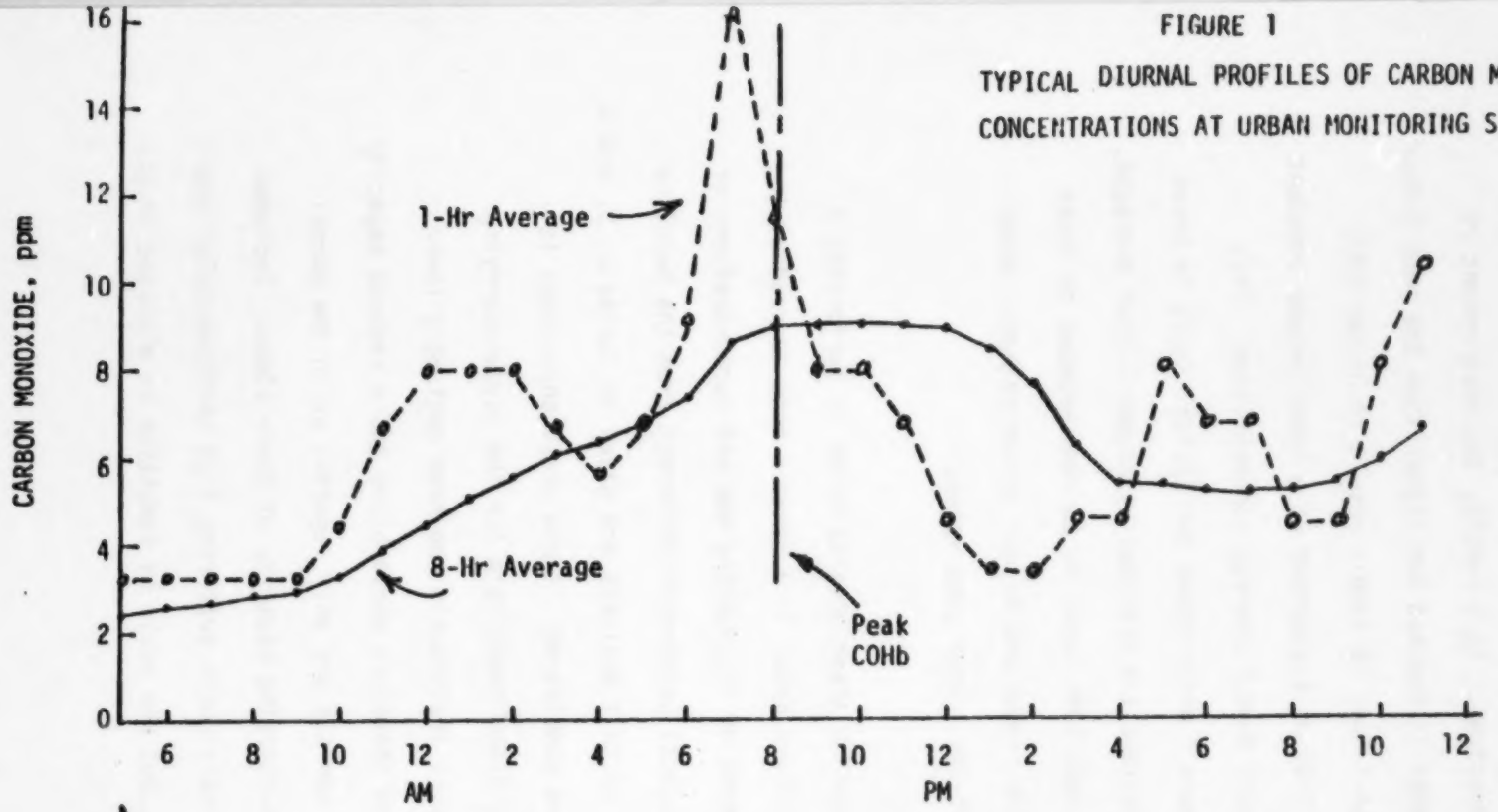
SENSITIVITY ANALYSIS

An attempt was made to represent these uncertainties by performing a sensitivity analysis using the Coburn model in a dynamic mode to predict the COHb responses to specific patterns of fluctuating ambient concentrations of CO for individuals with physiological parameters different from the baseline values of Table 1. The results of this analysis are given in Tables 2, 3, and 4.

Two types of individuals are considered: those whose physiology is in a normal range with regard to blood hemoglobin (or the oxygen-carrying capacity of their blood) and anemic individuals who have decidedly lower than normal hemoglobin levels and therefore whose blood has a reduced capacity to carry oxygen. The so-called normals are only regarded as in the normal range with respect to the oxygen-carrying capacity of their blood. Included as normal, therefore, would be individuals suffering from cardiovascular heart disease who are not also anemic, but who would be sensitive to elevated levels

FIGURE 1

TYPICAL DIURNAL PROFILES OF CARBON MONOXIDE CONCENTRATIONS AT URBAN MONITORING SITE



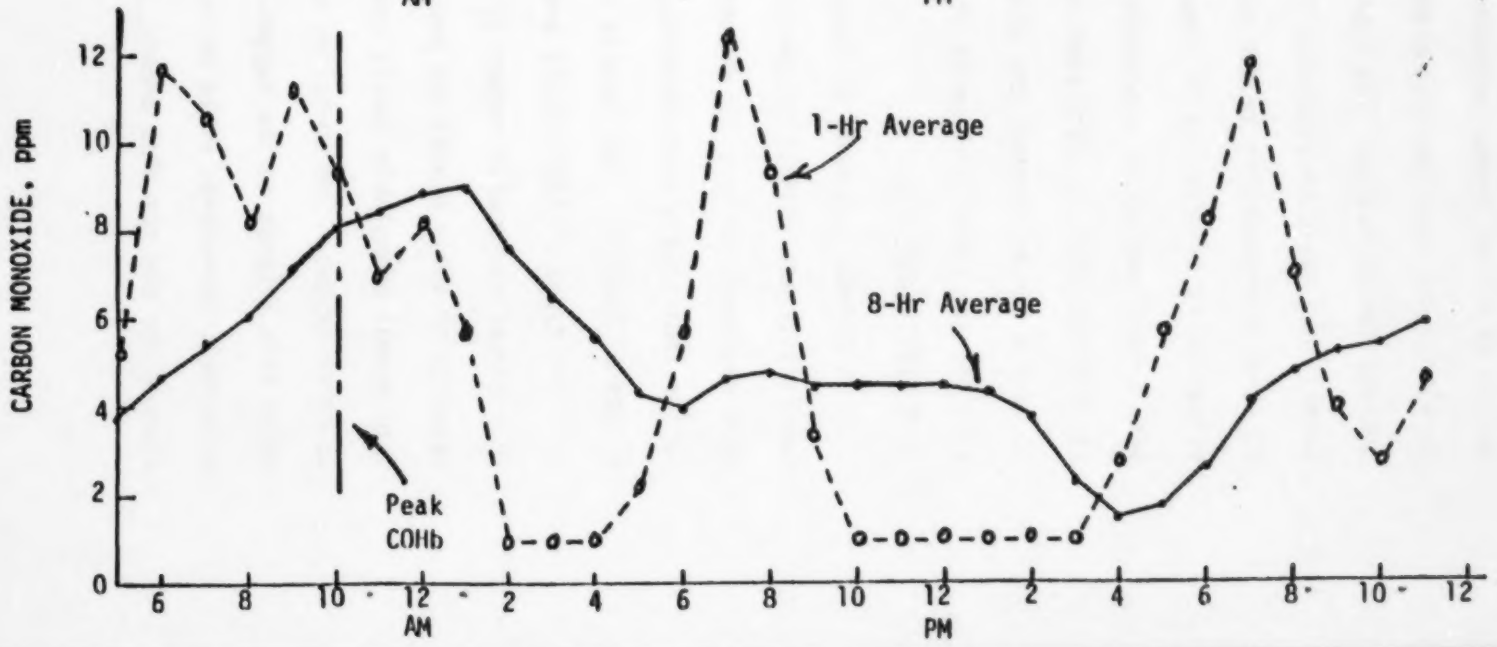


TABLE 2

COBURN MODEL ESTIMATES OF COHb LEVELS ASSOCIATED WITH ALTERNATIVE 1-HOUR CO STANDARD LEVELS

Standard Level,	COHb Levels (%) Predicted for a Range of Ventilation Rates for Exposure to the Maximum 1-Hour Average CO Concentration Permitted by the Specified Standard[a]				
	Case 1 Baseline or nominal physiological parameters	Case 2 High range of physiological parameters for normal persons (sea level)	Case 3 Same as Case 2, except assumes initial elevated COHb (1.5%) from external sources	Case 4 High range of physiological parameters for normal persons (5000 ft)	Case 5 Typical hemolytic anemic
20	1.1 - 1.4	1.8 - 2.2	2.3 - 2.6	1.8 - 2.2	2.7 - 2.9
25	1.3 - 1.6	2.1 - 2.6	2.6 - 3.0	2.1 - 2.6	3.0 - 3.3
35	1.6 - 2.1	2.7 - 3.5	3.2 - 3.9	2.7 - 3.5	3.6 - 4.1

[a] Coburn model parameters are as presented for Table 2, except a range of alveolar ventilation rates is presented. The lower value represents rest/intermittent light activity (V_A = 10 L/min) and the higher value represents moderate exercise (V_A = 20 L/min).

TABLE 3

COBURN MODEL ESTIMATES OF COHb LEVELS ASSOCIATED WITH ATTAINMENT OF ALTERNATIVE 8-HOUR CO STANDARD LEVELS[a,b]

Standard Level, ppm	Maximum 1-Hour Average COHb Levels (%) Predicted on Day When Annual Maximum 8-Hour CO Concentration Occurs, for a Range of Actual Air Quality Patterns Adjusted to Simulate Attainment of the Specified Standard			
	Case 1	Case 2	Case 3	Case 4
	Baseline or nominal physiological parameters	High range of physiological parameters for normal persons (sea level)	High range of physiological parameters for normal persons (5000 ft)	Typical hemolytic anemic individual
7	1.2 - 1.3	1.6 - 1.8	1.8 - 2.0	2.1 - 2.3
9	1.5 - 1.7	2.0 - 2.3	2.2 - 2.5	2.4 - 2.7
12	1.9 - 2.2	2.5 - 2.9	2.8 - 3.2	3.0 - 3.3
15	2.3 - 2.6	3.1 - 3.5	3.4 - 3.9	3.5 - 3.9

[a]COHb responses to fluctuating CO concentrations were dynamically evaluated using the Coburn model prediction of the COHb resulting from one hour's exposure as the initial COHb level for the next hour.

[b]Coburn model parameters:

Case 1: As given in Table 1, except only V_A = 10 L/min.

Case 2: V_A = 10 L/min; Hb = 13 g/dL; altitude = sea level; initial COHb = 0.7%; V_{co} = 0.014 mL/min; V_b = 3500 mL; $D_{L_{co}}$ = 40 mL/(min-mm Hg); M = 246.

Case 3: Same as Case 2, except altitude = 5000 ft.

Case 4: V_A = 10 L/min; Hb = 9 g/dL; altitude = sea level; initial COHb level = 1.9%; V_{co} = 0.030 mL/min; V_b = 4600 ml; $D_{L_{co}}$ = 25 mL/(min-mm Hg); M = 246.

TABLE 4

COBURN MODEL ESTIMATES OF COHb LEVELS ASSOCIATED WITH ATTAINMENT OF ALTERNATIVE 8-HOUR CO STANDARD LEVELS[a,b]

Standard Level, ppm	Maximum 1-Hour Average COHb Levels (%) Predicted on Day When Annual Maximum 8-Hour CO Concentration Occurs, for a Range of Actual Air Quality Patterns Adjusted to Simulate Attainment of the Specified Standard			
	Case 1	Case 2	Case 3	Case 4
	Baseline or nominal physiological parameters	High range of physiological parameters for normal persons (sea level)	High range of physiological parameters for normal persons (5000 ft)	Typical hemolytic anemic individual
7	1.2 - 1.5	1.6 - 2.0	1.8 - 2.2	2.1 - 2.5
9	1.4 - 1.9	2.0 - 2.6	2.2 - 2.8	2.4 - 3.0
12	1.8 - 2.4	2.5 - 3.3	2.8 - 3.6	3.0 - 3.7
15	2.3 - 3.0	3.0 - 4.1	3.3 - 4.4	3.5 - 4.4

[a] COHb responses to fluctuating CO concentrations were dynamically evaluated using the Coburn model prediction of the COHb resulting from one hour's exposure as the initial COHb level for the next hour. Twenty sets of 1-hour average CO concentrations were evaluated.

[b] Coburn model parameters:

Case 1: As given in Table 1, except only V_A = 10 L/min.

Case 2: V_A = 10 L/min; Hb = 13 g/dL; altitude = sea level; initial COHb = 0.7%; V_{co} = 0.014 mL/min; V_b = 3500 mL; $D_{L_{co}}$ = 40 mL/(min-mm Hg); M = 246.

Case 3: Same as Case 2, except altitude = 5000 ft.

Case 4: V_A = 10 L/min; Hb = 9 g/dL; altitude = sea level; initial COHb level = 1.9%; V_{co} = 0.030 mL/min; V_b = 4600 ml; $D_{L_{co}}$ = 25 mL/(min-mm Hg); M = 246.

of COHb because of their cardiovascular disease. The baseline case is taken as representing individuals whose physiological parameters with regard to the oxygen carrying-capacity of the blood are in the mid-range of normal. The high-normal case represents individuals who, although in the normal range, have physiological parameters which differ from the baseline values in directions that increase the COHb response to CO exposures. The parameters used for these cases seem reasonable since each value lies within the range reported in the literature as normal, as shown in Table 5.

Table 2, which covers alternative 1-hour standards, includes cases within the "normal range" at both sea level and 5000 feet in order to show the effect of altitude in increasing COHb levels at a given CO exposure. Case 3 shows the effect of exposure to ambient CO at the level of a standard after COHb levels have already been elevated due to exogenous sources (e.g., passive smoking). The ranges shown for each case correspond to the two alveolar ventilation rates shown for each of the standard averaging times in Table 1.

The Coburn model was used in a dynamic mode to calculate the data in Table 3 which covers alternative levels of the 8-hour standard. The basis for the dynamic calculation is set forth below. Because of its complexity, the differential equation which underlies the Coburn equation is typically solved for static situations (see Appendix for discussion of the Coburn equation). That is, it is assumed an individual is exposed to a constant level of CO over the period of the exposure. It is possible, however, to use the static solution to treat the dynamic conditions normally experienced in the ambient situation. By taking a sufficiently short time period, the average concentration of CO over the period can be substituted into the static equation along with the blood level of COHb at the start of the period to obtain a good estimate of the COHb at the

Table 5

RANGES FOR COBURN MODEL PARAMETERS

1. HALDANE CONSTANT: Relative affinity of hemoglobin for CO and oxygen:
   Range: 210-250 (refs. 6-11)

2. INITIAL COHB: COHb level before exposure.
   Normal Range: 0.3-0.7% (ref. 12)
   Hemolytic Anemics: 0.8-2.7% (refs. 2, 13)

3. ENDOGENOUS CO PRODUCTION RATE: Internal CO production from metabolic breakdown of hemoglobin.
   Normal Range: 0.007-0.014 ml/min (refs. 12,13)
   Hemolytic Anemics: 0.012-0.057 ml/min (refs. 2, 13)

4. BLOOD VOLUME:
   Normal Range: 3500-7500 ml (ref. 5)

5. HEMOGLOBIN: Quantity of hemoglobin per unit volume of blood.
   Normal Range: 11-17 g/100ml (refs. 5,14)
   Hemolytic Anemics: 6-13 g/100ml (refs. 2,13)

6. LUNG DIFFUSIVITY: Rate of diffusion of CO from lung into the blood.
   Normal Range: 18-45 ml/min/Torr (refs. 5,15)

end of the period. A 1-hour time period is approximately an upper limit for obtaining reliable estimates. This period is, of course, convenient since it is a commonly recorded time average for air quality data.

Given a number of successive 1-hour average CO exposures, only the COHb level at the start of the first hour needs to be known, since the calculated COHb at the end of each hour becomes the starting level for the next hour. Furthermore, the initial COHb for the first hour has a declining effect on the succeeding hours, becoming negligible after about ten hours. Thus the assumption of an initial value for COHb, which is an important consideration in static calculations, has little to no importance in dynamic calculations involving extended series of consecutive 1-hour CO concentrations.

The ability of the Coburn model to adequately integrate exposures to varying CO concentrations has been evaluated by Peterson and Stewart in limited experimentation (4,5) with good results.

The dynamic approach was applied to estimating peak COHb levels which might occur in an individual exposed to peak levels of ambient CO which just reached the level of an 8-hour national ambient air quality standard. In order to obtain realistic profiles of CO levels during peak periods, monitoring data were obtained over a forty hour period at each of five representative sites during episodes of high CO. Eight-hour running average concentrations were calculated from the successive 1-hour average concentrations for each site. Both the 1 and 8-hour concentrations were then proportionally rolled back (taking background CO into account) so that the peak value of the 8-hour CO concentrations over the last twenty-four hours just met one of the alternative standard levels of the study. The sets of successive rolled

back 1-hour concentrations were then used to calculate the COHb levels in a hypothetical individual experiencing the given exposure pattern. Figure 1 shows the rolled back CO concentrations for the sites which gave the highest and lowest peak COHb levels. They are the upper and lower plots, respectively. The plots also show the hour in which the peak COHb occurred. The time of occurrence did not change with choice of physiological parameters used in the Coburn model over the parameter range investigated.

The ranges that appear in Table 3 for each case are the ranges of COHb values obtained from the five different sets of CO data. As indicated above, the same sets (Figure 1) always led to the highest and lowest peak COHb values and thus determined the ranges shown. Comparison of the baseline numbers for the 8-hour case in Tables 1 and 3 shows that the range of the dynamic calculations is above the values of the static calculation. As discussed above, this comes about from the high 1-hour concentrations experienced just before a peak occurs in the running 8-hour calculations (Figure 1). Another difference between the data in Table 3 and in the previous tables is that there is no need to assume an initial value for the COHb level in the dynamic calculation.

At a later time, the number of CO air quality patterns studied using the dynamic calculation was expanded from five to twenty. Table 4 shows the results obtained with the patterns in the set of twenty which gave the highest and lowest COHb values in the dynamic calculation. It is seen that the lower bound numbers in the ranges shown in both Tables 3 and 4 are very similar, while the higher bounds of the ranges in Table 4 are distinctly greater than in Table 3. This probably comes from the fact that peak 8-hour averages that result from a relatively constant sequence of 1-hour concentrations

similar in magnitude to the 8-hour average occur fairly frequently and lead to relatively low COHb levels. High COHb levels occur when the primary contribution to the peak 8-hour average is from a much higher 1-hour peak that immediately preceeds it. These CO patterns appear to occur less frequently than the relatively flat variety.

DISTRIBUTION OF COHb LEVELS IN SENSITIVE POPULATIONS

The ranges of the physiological parameters shown in Table 5 for "normal" individuals and those with hemolytic anemia were used to make rough estimates of how the COHb levels in persons with cardiovascular diseases would be distributed if each person were exposed to the same constant CO level for one hour or the same changing set of CO levels for over ten or more hours. To make this calculation, it was assumed that measurements of the Coburn model physiological parameters in random samplings of "normal" persons with cardiovascular heart disease would yield the familiar bell-shaped or normal distribution of the parameters. The same assumption was also made for the parameters of persons with both hemolytic anemia and cardiovascular heart disease. It was further assumed that the widths of the ranges given in Table 5 for "normal" persons and persons with hemolytic anemia represent either four or six standard deviations of the distributions (the 2 and 3 sigma limits, respectively). The mean value of each parameter would be at the center of its range.

Analyses performed on available literature data suggested that the physiological parameters were statistically independent of one another with one exception. The lung diffusivity and blood volume parameter appeared to correlate with an $r^2 = 0.98$.

A computer program was developed which made a random selection of a set of parameters based on the assumption that they were normally distributed with means and standard deviations determined (as discussed above) from the ranges in Table 5. The lung diffusivity value was not determined by random sampling but calculated from the randomly determined blood volume using a linear regression of lung diffusivity on blood volume (based on data in Table 1 of reference 5). In the case of a 1-hour static calculation, the randomly selected parameters along with the CO standard level, ventilation rate (which was not randomized) and the altitude were substituted into the static Coburn model to calculate the COHb level. In the case of a dynamic calculation, a CO concentration pattern of 1-hour averages over at least fifteen hours was used. Also, in the dynamic case, the randomly selected initial COHb value was ignored since it had no significant effect on the calculated final COHb level. This process of random selection of parameters and computation of corresponding COHb levels was repeated in the computer many times, each time with a different set of randomly chosen physiological parameters. During this process, CO levels, ventilation rate, and altitude were held constant. The result was a large collection of COHb values whose distribution was, under the above assumptions, expected to be the same as that in a population of exposed people.

With this procedure, it was possible to estimate the distribution of COHb blood levels resulting from any set of static or dynamic exposure conditions. Tests on a number of the COHb distributions derived in this manner showed that they were also distributed normally to a close approximation. It was therefore possible to determine the mean and standard deviation of the COHb distribution, and from the properties of the normal curve estimate the fraction of a sensitive population which would experience COHb levels at or above any given level under the specified conditions of exposure.

TABLE 6

CUMULATIVE PERCENT OF SENSITIVE PERSONS WITH COHb ≥ SPECIFIED FINAL COHb VALUE, WHEN EXPOSED TO AIR QUALITY ASSOCIATED WITH ALTERNATIVE STANDARDS

(Cardiovascular Heart and Peripheral Vascular Disease)****

Final COHb (Percent)*	Dynamic Calculation**			Static Calculation***		
	7 ppm, 8-Hr	9 ppm, 8-Hr	12 ppm, 8-Hr	20 ppm, 1-Hr	25 ppm, 1-Hr	30 ppm, 1-Hr
2.9			<0.01			
2.7			<0.4			
2.5			0-13			<0.2
2.3		<0.01	0.5-71		<0.01	0.4-4
2.1		<0.5	39-100		<0.6	18-30
1.9	<0.01	0.01-25	100	< 0.1	4-13	74-81
1.7	<0.6	16-97	100	0.4-5	61-64	96-100
1.5	0.07-36	91-100	100	36-44	95-100	100
1.3	64-100	100	100	91-97	100	100

*Assumes all physiological inputs to Coburn equation are normally distributed in the sensitive population.

**COHb responses to fluctuating CO concentrations were dynamically evaluated using the Coburn model prediction of the COHb resulting from one hour's exposure as the initial COHb level for the next hour. These results are based on on alveolar ventilation rate of 10 L/min (intermittent rest/light activity).

***COHb levels calculated based on constant level exposure and an alveolar ventilation rate of 20 L/min (moderate activity).

****Estimated total cardiovascular heart disease and peripheral vascular disease population is 7,700,000.

Table 6 summarizes the estimated distribution of COHb levels in persons with cardiovascular heart disease under exposure to air quality associated with alternative 1-hour and 8-hour standards. For this and subsequent tables, exposure is assumed to occur at sea level. From the point of view of the calculation, two populations are involved. The first consists of persons with cardiovascular heart disease or peripheral vascular disease who are in the normal range with regard to oxygen-carrying capacity of the blood. The second consists of persons with cardiovascular heart disease or peripheral vascular disease who also have hemolytic anemia. The COHb distributions are determined for each population separately and then combined in proportion to the numbers of persons in each group. The number of persons who have angina and other types of cardiovascular diseases has been estimated by the U.S. National Health Examination Survey (NHES),[17] which during 1960 through 1962 examined a sample of the civilian non-institutionalized population aged 18 to 79 years to obtain information on the prevalence of cardiovascular and other diseases. The Survey estimated that 5.0 percent of the adult population had definite or suspected coronary heart disease. The adult population aged 18 to 79 years is estimated to be 140 million in 1979.[18,19] Multiplying this population by the cardiovascular incidence rate, results in an estimate of 7.0 million individuals with cardiovascular heart disease. Another 0.34% of the total population are estimated to have peripheral vascular disease or 0.7 million individuals.[20] This results in a combined population estimate of 7.7 million individuals with cardiovascular heart disease or peripheral vascular disease.

The estimated size of the second population of concern, those with cardiovascular heart or peripheral vascular disease who also are hemolytic

anemics, is derived as follows. A 1973 National Health Interview Survey[21] estimates that specific anemias having a hemolytic component occur in 0.04 to 0.11 percent of the U.S. population. Assuming independence (i.e. assuming that anemia does not predispose a person to have cardiovascular or peripheral vascular disease), the cardiovascular (or peripheral vascular) - hemolytic anemia intersection would be estimated to consist of approximately 3,000 to 8,000 persons nationwide. A medical scientist on the CASAC CO Subcommittee has suggested that the estimates for the intersection group be reduced by a factor of 10, based on the fact that most cardiovascular patients are over age 40 and the vast majority of hemolytic anemic individuals are under 40. The resulting estimate used in this sensitivity analysis is 310 to 850 individuals with cardiovascular or peripheral vascular disease and hemolytic anemia.

Table 6 shows a range of values for each COHb level and set of exposure conditions. This results from several uncertainties in the input information. At each set of exposure conditions (specified by the standard level, the averaging time of the standard, the alveolar ventilation rate, and the altitude) there was uncertainty concerning the number of hemolytic anemics with cardiovascular heart disease (310 to 850 persons), the choice of standard deviation for each of the physiological parameter distributions (2- or 3-sigma limits) and, in the case of the dynamic calculation, the choice of the upper or lower bound air quality pattern (Figure 1). These uncertainties were treated by obtaining the distributions for each set of exposure conditions for all possible combinations of assumptions on the limiting values of the uncertain quantities.

For example, a distribution would be calculated for a given 8-hour standard assuming the lower bound estimate for the hemolytic anemic population, the 2-sigma limit for the physiological parameters, and the upper bound CO pattern. The distribution would then be calculated again with a different combination of assumptions, etc., until all combinations had been exhausted. The ranges reported in the tables at each COHb level and exposure condition are the lowest and highest number of people that were calculated by this procedure.

For the data in Table 6, the patterns were the upper and lower bound patterns for the original five sets of CO data that were examined. When the number of patterns was subsequently expanded to twenty, these original bounding patterns were found to be roughly at the $\pm$ 1-sigma of the set of twenty in terms of the COHb levels they produced.

Examination of the distribution data for the 1-hour standard in Table 6 shows that there are likely to be very few people exhibiting the high levels of COHb shown for "high normal" in Table 2 under the given exposure conditions. The reason for this is that the physiological parameters of the "high normal" individual are all at the ends of their respective ranges and even with the 2-sigma limit assumption the occurence of such an individual in the population is rare (roughly 3 people in 10 million).

A related observation is the narrowness of the distributions. There is a rapid change in the number of people over relatively short ranges of COHb. This is primarily explained by the 2 and 3-sigma limit assumptions which, essentially by the same mechanism operative in the last paragraph, strongly limit the range of the resulting COHb distribution.

Table 7 gives estimated expected values for the distribution of COHb levels in the same population. For the 8-hour standard, a single CO pattern was chosen from the set of twenty. The calculated COHb level which this pattern gave was closest to the average of the twenty patterns. For both the 8-hour and 1-hour standards, it was assumed the 2-sigma limit assumption on the range of physiological parameters was more apt to be correct than the 3-sigma limit assumption. Given the relatively small data base examined in deciding on the ranges of the physiological parameters shown in Table 5, it was judged that the 3-sigma limit was more likely to be an upper bound and that a suitable lower bound would be lower than the 2-sigma limit. Consequently, in calculating the expected distribution, the 2-sigma limit assumption was used.

It was also assumed that 0.0075% or about 580 persons with cardiovascular heart disease also have hemolytic anemia. These values are the midpoints of the ranges given above for these numbers.

The values within the parentheses in Table 7 are the values obtained when the upper and lower bound CO patterns from the first set of five patterns were used in the calculations. As indicated above, these patterns give COHb levels at roughly the 1-sigma limits of the larger set of twenty patterns and thus define the range of COHb values that would be obtained by about two/thirds of the patterns of CO concentrations leading to peak 8-hour averages.

Table 8 shows the expected distributions for hemolytic anemics with cardiovascular disease. These values were extracted from the calculations leading to Table 7, except that the relative frequencies were converted to numbers of people.

Table 9 shows the effect of assuming an initial COHb level of 1.5% for the entire sensitive population due to exogenous sources. In this case, the computer program was modified to use the fixed value of 1.5% for initial COHb instead of a randomly selected value.

TABLE 7

CUMULATIVE PERCENT OF SENSITIVE PERSONS WITH COHb ≥ SPECIFIED FINAL COHb VALUE, WHEN EXPOSED TO AIR QUALITY ASSOCIATED WITH ALTERNATIVE STANDARDS

(Cardiovascular Heart and Peripheral Vascular Disease)[a]

Final COHb (Percent)[b]	Dynamic Calculation[c]			Static Calculation[d]		
	7 ppm, 8 hr	9 ppm, 8 hr	12 ppm, 8 hr	20 ppm, 1 hr	25 ppm, 1 hr	30 ppm, 1 hr
2.9			.01 (<.01)			<.01
2.7			.2 (<.01-.4)			.01
2.5			6 (.1-13)		<.01	.2
2.3		<.01 (<.01)	43 (5-66)		.01	4
2.1		.2 (<.01-.5)	89 (47-97)	<.01	.6	29
1.9	<.01 (<.01)	13 (.6-25)	99 (93-100)	.1	13	73
1.7	.2 (<.01-.6)	73 (28-89)	100 (100)	5	61	95
1.5	20 (2-36)	99 (91-100)	100 (100)	44	95	100
1.3	89 (63-97)	100 (100)	100 (100)	91	100	100

[a]Estimated total cardiovascular heart disease and peripheral vascular disease population is 7,700,000.

[b]Assumes all physiological inputs to Coburn equation are normally distributed in the sensitive population.

[c]COHb responses to fluctuating CO concentrations were dynamically evaluated using the Coburn model prediction of the COHb resulting from 1 hour's exposure as the initial COHb level for the next hour. The series of 1-hour CO concentrations used was a representative pattern selected from 20 sets of actual air quality data that just reached the level of the specified 8-hour standard. These results are based on alveolar ventilation rate of 10 L/min (intermittent rest/light activity). Numbers in parentheses were calculated using CO patterns which lead to COHb levels at ± one standard deviation from the mean for all of the CO patterns studied.

[d]COHb levels calculated on the basis of constant level exposure and an alveolar ventilation rate of 20 L/min (moderate activity).

TABLE 8

CUMULATIVE NUMBER OF SENSITIVE PERSONS WITH COHb ≥ SPECIFIED FINAL COHb VALUE, WHEN EXPOSED TO AIR QUALITY ASSOCIATED WITH ALTERNATIVE STANDARDS

(Cardiovascular Heart Disease with Hemolytic Anemia)[a]

Final COHb (Percent)[b]	Dynamic Calculation[c]			Static Calculation[d]		
	7 ppm, 8-Hr	9 ppm, 8-Hr	12 ppm, 8-Hr	20 ppm, 1-Hr	25 ppm, 1-Hr	30 ppm, 1-Hr
2.9	2	70	430	170	390	520
2.7	10	180	520	300	480	560
2.5	60	320	560	420	540	570
2.3	160	460	570	510	570	580
2.1	320	540	580	560	580	580
1.9	470	570	580	570	580	580
1.7	550	580	580	580	580	580
1.5	570	580	580	580	580	580
1.3	580	580	580	580	580	580

[a]Best estimate of the total cardiovascular heart disease and peripheral vascular disease population with hemolytic anemia is 580.

[b]Assumes all physiological inputs to Coburn equation are normally distributed in the sensitive population.

[c]COHb responses to fluctuating CO concentrations were dynamically evaluated using the Coburn model prediction of the COHb resulting from one hour's exposure as the initial COHb level for the next hour. The series of 1-hour CO concentrations used was representative pattern selected from 20 sets of actual air quality data that just reached the level of the specified 8-hour standard. These results are based on an alveolar ventilation rate of 10 L/min (intermittent rest/light activity).

[d]COHb levels calculated based on constant level exposure and an alveolar ventilation rate of 20 L/min (moderate activity).

TABLE 9

CUMULATIVE PERCENT OF SENSITIVE PERSONS WITH COHb ≥ SPECIFIED FINAL COHb VALUE, WHEN EXPOSED TO AIR QUALITY ASSOCIATED WITH ALTERNATIVE STANDARDS AND GIVEN HIGH INITIAL COHb DUE TO PREVIOUS EXPOSURE[a]

(Cardiovascular Heart and Peripheral Vascular Disease)[b]

Final COHb (Percent)[c]	Static Calculation[d] 20 ppm, 1 hr	25 ppm, 1 hr	30 ppm, 1 hr
2.9		< .01	6
2.7		0.4	51
2.5	<.01	27	94
2.3	5	92	100
2.1	83	100	100
1.9	100	100	100
1.7	100	100	100
1.5	100	100	100
1.3	100	100	100

[a]Assumes initial COHb level of 1.5% for entire sensitive population due to exogenous sources.

[b]Estimated total cardiovascular heart disease and peripheral vascular disease population is 7,700,000.

[c]Assumes all physiological inputs to Coburn equation are normally distributed in the sensitive population.

[d]COHb levels calculated based on constant level exposure and an alveolar ventilation rate of 20 L/min (moderate activity).

REFERENCES

1. U.S. Environmental Protection Agency. Preliminary Assessment of Adverse Health Effects from Carbon Monoxide and Implications for Possible Modifications of the Standard. Draft Staff Paper presented at the meeting of the Science Advisory Board's Clean Air Scientific Advisory Committee, June 14-16, 1979.

2. Coburn, R.F., R.E. Forster, and P.B. Kane. Considerations of the physiology and variables that determine the blood carboxyhemoglobin concentration in man. J. Clin. Invest. 44: 1899-1910, 1965.

3. Ott, W., and D. Mage, Interpreting urban carbon monoxide concentrations by means of a computerized blood COHb model. Presented at the 67th Annual Meeting of the Air Pollution Control Association, Denver, Colorado, June 9-13, 1974.

4. Peterson, J.E., and R.D. Stewart. Absorption and elimination of carbon monoxide by inactive young men. Arch. Environ. Health 21: 165-171, 1970.

5. Peterson, J.E., and R.D. Stewart. Predicting the carboxyhemoglobin levels resulting from carbon monoxide exposures. J. Appl. Physiol. 39(4): 633-638, 1975.

6. Sendroy, J., Jr., S.H. Liu, and D.D. Van Slyke. The gasometric estimation of the relative affinity constant for carbon monoxide and oxygen in whole blood at 38°. Amer. J. Physiol. 90: 511, 1929.

7. Sendroy, J., Jr., and J.D. O'Neal. Relative affinity constant for carbon monoxide and oxygen in blood. Fed. Proc. 14: 137, 1955.

8. Rodkey, F.L., J.D. O'Neal, and H.A. Collison. Oxygen and Carbon monoxide equilibria of human adult hemoglobin at atmospheric and elevated pressure. Blood 33 (1): 57-65, 1969.

9. Roughton, F.J.W. The equilibrium of carbon monoxide with human hemoglobin in whole blood. Ann. N.Y. Acad. Sci. 174: 177-188, 1970.

10. Joels, N., and L.G.C.E. Pugh. The carbon monoxide dissociation curve of human blood. J. Physiol. (London) 142: 63-77, 1958.

11. Haldane, J., and J.L. Smith. The absorption of oxygen by the lungs. J. Physiol. (London) 22: 231, 1897.

12. Coburn, R.F., W.S. Blakemore, and R.E. Forster. Endogenous carbon monoxide production in man. J. Clin. Invest. 42: 1172-1178, 1963.

13. Logue, G.L., W.F. Rosse, W.T. Smith, H.A. Saltzmann, and L.A. Gutterman. Endogenous carbon monoxide production measured by gas-phase analysis: An estimation of heme catabolic rate. J. Lab. Clin. Med. 77: 867-876, 1971.

14. "Hemoglobin and selected iron-related findings of persons 1-74 years of age: United States, 1971-1974." Advance data Number 46, U.S. Department of Health, Education, and Welfare, Public Health Service. January 26, 1979.

15. Forster, R.E. Diffusion of gases. In: Handbook of Physiology. Respiration. Washington, D.C.: Am. Physiol. Soc., 1975, Sect. 3, Vol. 1, Chap. 33, pp. 839-872.

16. Coburn, R.E. Personal communication with Don Lokey, U.S. EPA, September 1979.

17. U.S. Department of Health, Education, and Welfare (DHEW), Public Health Service. Coronary Heart Disease in Adults, United States: 1960-1962. DHEW Publication No. (PHS) 79-1019. Hyattsville, Maryland. December 1975.

18. 1979 Commercial Atlas and Marketing Guide. Rand McNally and Company. Chicago, Illinois. 1979.

19. U.S. Department of Commerce, Bureau of the Census. Characteristics of the Population. Washington, D.C. 1973.

20. U.S. Department of Health, Education, and Welfare (DHEW). Prevalence of Chronic Circulatory Conditions: United States, 1972. DHEW Publication No. (HRA) 75-1521. Rockville, Maryland. 1974.

21. U.S. Department of Health, Education, and Welfare (DHEW). Prevalence of Chronic Conditions of the Genitourinary, Nervous, Endocrine, Metabolic, and Blood and Blood-Forming Systems and other Selected Chronic Conditions: United States, 1973. DHEW Publication No. (HRA) 77-1536. Rockville, Maryland. 1977.

APPENDIX

PROCEDURE FOR CALCULATION OF CARBOXYHEMOGLOBIN LEVEL IN BLOOD

The following symbols are used in this discussion:

$d(CO)/dt$	Rate of change of carbon monoxide (CO) in the body, ml/min at STP.
$[COHb]$	Concentration of COHb in the blood at time t, ml CO/ml Blood.
$[COHb]_o$	Concentration of COHb at t=0, ml/ml.
$[O_2Hb]$	Concentration of oxyhemoblogin in the blood at time t, ml of oxygen, ml/ml.
$(\%COHb)$	Concentration of COHb as percent saturation.
$(\%COHb)_o$	Concentration of COHb at t=0 as percent saturation.
$(\%O_2Hb)$	Concentration of O_2Hb as percent saturation.
(CO)	Concentration of inspired CO, ppm.
p_ICO	Inspired CO pressure, torr.
p_cO_2	Mean pulmonary capillary oxygen pressure, torr.
p_IO_2	Inspired oxygen pressure, torr.
P_B	Barometric pressure, torr.
pH_2O	Vapor pressure of water at body temperature, torr. Has the value 47 torr.
$\dot{V}_A$	Alveolar ventilation rate, ml/min.
$\dot{V}_{CO}$	Endogenous rate of CO production, ml/min.
M	Haldane constant.
D_L	Diffusion rate of CO in the lungs, ml/min/torr.
V_b	Blood volume, ml.
Hb	Hemoglobin content of blood, g/100ml.
Alt	Altitude above sea level, ft.

Coburn, Forster, and Kane (1) derived the following differential equation governing COHb levels in the blood:

$$d(CO)/dt = \dot{V}_{CO} + p_I CO/B - [COHb]*A/B$$

where

$$A = p_c O_2/(M*[O_2Hb])$$

$$B = (1/D_L) + (P_B - pH_2O)/\dot{V}_A$$

The use of the terms A and B follows the treatment of Peterson and Stewart (2).

If it is assumed that total body stores of CO are proportional to [COHb] and are equal to the product of [COHb] and the effective blood volume, Vb, and only [COHb] changes in the time interval t then the above equation can be integrated to yield the following solution:

$$A*[COHB] - B*V_{CO} - p_I CO =$$

$$(A*[COHb]_o - B*V_{CO} - P_I CO)*\exp(-t*A/(Vb*B))$$

This expression is referred to as the CFK equation after its developers Coburn, Forster, and Kane.

It is customary to express COHb levels in percent of saturation (maximum possible level of COHb). Since a gram of hemoglobin can combine with as much as 1.38 ml of CO as COHb, the maximum level is 1.38*Hb/100 given the above units for Hb. Thus

$$(\%COHb) = 10^4*[COHb]/(1.38*Hb)$$

Since the capacity for oxyhemoglobin is also 1.38*Hb/100 it is also true that:

$$(\%O_2Hb) = 10^4*[O_2Hb]/(1.38*Hb)$$

If the term A is redefined in terms of $(\%O_2Hb)$:

$$A = p_c O_2/(M*(\%O_2Hb)) \qquad \text{(new definition)}$$

and if CO is expressed as concentration in parts per million, the CFK equation becomes:

$$A*(\%COHb) - B*\dot{V}_{CO} - P_B*10^{-6}*(CO)=$$

$$(A*(\%COHb)_o - B*\dot{V}_{CO} - P_B*10^{-6}*(CO))*\exp(-t*A*10^4/(1.38*Hb*Vb*B))$$

which on further rearranging gives:

$$(\%COHb) = (\%COHb)_o*F + (B*\dot{V}_{CO} + P_B*10^{-6}*(CO))*(1-F)/A$$

where

$$F = \exp(-t*A*10^4/(1.38*Hb*Vb*B))$$

To apply the CFK equation it is convenient to have the average pulmonary capillary pressure of oxygen in terms of pressure of oxygen in the inspired air. This relationship is (3):

$$p_cO_2 = p_IO_2 - 46.9$$

The pressure in inspired air then can be related to the total pressure as follows:

$$p_IO_2 = 0.209*(P_B - pH_2O - p_ICO)$$

In the calculations performed in the study the partial pressures of CO were small enough to be dropped from the expression.

The study was also concerned with the effect of altitude on COHb levels. The effect on the CFK equation is primarily through the change in barometric pressure (3):

$$P_B = 760*\exp(-0.000386*Alt)$$

The accuracy of the COHb value calculated from the CFK equation can be improved by taking into account the change in O_2Hb which must accompany any change in COHb. The two quantities are related by:

$$(\%COHb) + (\%O_2HB) = 100$$

Peterson and Stewart (2) used this relationship as the basis for an iterative correction to the CFK equation.

$$\text{New } (\%O_2Hb) = 100*(\%O_2Hb)/((\%O_2Hb) + (COHb)$$

The variables on the right side of the above equation result from one iteration and are used to calculate the O_2Hb value to be input into the next iteration. In the initial iteration the O_2Hb value is taken as 100%. Further iteration is stopped when successive calculations produce no sensible change in the calculated COHb level. For the levels of COHb investigated in the study (<5%) there is no sensible affect an the validity of the CFK equation.

Table A-1 shows the algorithm used to calculate COHb levels given an initial value for the COHb level, the concentration of inspired CO, the altitude, and a set of values for the physiological parameters. The algorithm can be used directly for reasonable accuracy for exposure to changing concentrations of CO if a contiguous series of time averaged concentrations of CO are available and the time interval associated with each average is not greater than one hour. In this case an initial value of the COHb level is assumed at the start of the first time interval and the COHb level calculated at the end of the interval using the algorithm. This COHb level is used as the initial value of COHb for the next interval and the algorithm used again to calculate the COHb at the end of the second interval. This process is repeated until COHb values are obtained at the end of each interval in the series. If hourly averages are used, the COHb values after about 13 hours are essentially independent of the choice of the initial COHb level at the beginning of the first time interval.

TABLE A-1 ALGORITHM FOR CALCULATION OF CARBOXYHEMOGLOBIN IN BLOOD

1. Given the altitude, calculate average barometric pressure:

$$P_B = 760*\exp(-0.000368*Alt)$$

2. Calculate capillary oxygen pressure:

$$p_cO_2 = 0.209*(P_B-47) - 46.9$$

3. Calculate quantity B:

$$B = (1/D_L) + (P_B-47)/\dot{V}_A$$

4. Let $(\%O_2Hb) = 100$

5. Calculate A:

$$A = p_cO_2/(M*(\%O_2Hb))$$

6. Calculate F:

$$F = \exp(-t*A*60*10^4/(1.38*Hb*Vb*B))$$

7. Calculate trial (%COHb) value:

$$(\%COHb) = (\%COHb)_o*F + (B*V_{CO} + P_B*10^{-6}*(CO))*(1-F)/A$$

8. Calculate $(\%O_2Hb)$ value for next iteration:

$$\text{New } (\%O_2Hb) = 100*(\%O_2Hb)/((\%O_2Hb) + (\%COHb))$$

9. Starting with the new value of $(\%O_2Hb)$ repeats Steps #5 through #8. Compare the (%COHb) calculated with that from the previous iteration. Repeat cycle until two successive COHb values agree within the desired accuracy.

APPENDIX REFERENCES

1. Coburn, R.F., R.E. Forster, and P.B. Kane. Considerations of the physiology and variables that determine blood carboxyhemoglobin concentration in man. J. Clin. Invest. 44: 1899-1910, 1965.

2. Peterson J.E., and R.D. Stewart. Predicting the carboxyhemoglobin levels resulting from carbon monoxide exposures. J. Appl. Physiol. 39 (4): 633-638, 1975.

3. U.S. Environmental Protection Agency. Altitude as a Factor in Air Pollution. EPA-600/9-78-015, June 1978.